DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation and Research
1401 Rockville Pike
Rockville MD 20852-1448

Certified-Return Receipt Requested

Notice of Initiation of Disqualification Proceeding and Opportunity to Explain

APR 6 2000

Roy C. Page, M.D.
Mid-South Surgical Oncology Center
6005 Park Avenue, Suite 828-B
Memphis, Tennessee 38119-5223

Dear Dr. Page:

Between December 7 and 9, 1999, a Food and Drug Administration (FDA) investigator conducted an inspection of the following clinical studies in which you participated:

(1) _____ (hereafter, referred to as Protocol 1). This study was an extension of research previously conducted under the title _____

(2) _____ - (hereafter, referred to as Protocol 2).

This inspection was conducted as part of the FDA's Bioresearch Monitoring Program which includes inspections designed to monitor the conduct of research involving investigational products.

You responded in a letter dated December 22, 1999, to FDA Investigator Patricia Smith. Our comments regarding your responses are included below.

Based on our evaluation of information obtained by the Agency, we believe that you have repeatedly or deliberately violated regulations governing the proper conduct of clinical studies involving investigational products as published under Title 21, Code of Federal Regulations (CFR), Parts 312, 50, and 56 [21 CFR 312, 50, and 56]. Copies of these regulations are enclosed.

This letter provides you with written notice of the matters under complaint and initiates an administrative proceeding, described below, to determine whether you should be disqualified from receiving investigational products as set forth under 21 CFR § 312.70.

A listing of the violations follows. The applicable provisions of the CFR are cited for each violation.

1. **Failure to submit an Investigational New Drug Application (IND) to FDA and failure to withhold administration of an investigational new drug until an IND is in effect. [21 CFR §§ 312.20, 312.40(d), and 312.50].**

   You initiated Protocol 2 without filing an IND with the FDA. Our inspection determined that you administered an investigational serum/vaccine, referred to as ———— to at least three subjects during the period from September to December, 1999. There is no IND in effect for this investigational new drug which is composed of ————————————————obtained by an unapproved process and shipped through interstate commerce. Through your involvement with IND —— in April 1999, you became aware that an IND is required for such research.

   Your response letter dated December 22, 1999, acknowledges that you administered the investigational ———— to three subjects, one of whom later died, and that you provided the files for the remaining two subjects for FDA review. Your response letter states that Protocol 2 "is in the process of being developed;" however, you are not permitted to conduct the research in human subjects without an IND.

2. **Failure to fulfill the general responsibilities of investigators. [21 CFR § 312.60 and Part 50].**

   On May 20, 1999, you signed an FDA Form 1572 Statement of Investigator, in which you agreed to fulfill the requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

   Our investigation revealed that you did not fulfill your obligations as a clinical investigator in the use of unlicensed biological drugs and investigational new drugs in that:

   A. You failed to adequately protect the safety and welfare of subjects.

      i. You enrolled a subject who was not eligible according to the requirements stated in the protocol. See item 3A, below.

ii. You did not document the occurrence of adverse reactions, and you did not establish procedures to collect and summarize reports of adverse reactions associated with the investigational vaccine/serum.

B. You failed to adequately protect the rights of subjects.

i. The consent forms are broadly deficient; see item 7, below.

ii. You did not obtain the informed consent of subject —— enrolled in Protocol 2.

3. **Failure to follow the investigational plan. [21 CFR § 312.60].**

FDA documented numerous protocol violations in its review of subject records for Protocols 1 and 2. These violations include, but are not limited to, the following:

A. You enrolled a subject who was not eligible according to the criteria stated in Protocol 1. Subject—— had a platelet count of 144,000, but the protocol required a platelet count of greater than 150,000.

B. You administered the investigational serum/vaccine to subjects even though Protocols 1 and 2 prohibit the administration of concomitant investigational agents. The following are examples:

i. Subject —— was administered concomitant hyperthermia treatments and ———— under Protocol 1. ———— is not approved to treat cancer.

ii. Subject —— was administered hyperthermia under Protocol 1.

iii. Subject —— was administered concomitant ———— under Protocol 1.

iv. Subject —— was administered concomitant hyperthermia treatments in Protocol 2.

v. Subject —— was administered concomitant hyperthermia treatments in Protocol 2.

Your response letter dated December 22, 1999, states that concomitant therapies or treatments were "initially designed to include such treatment" in Protocol 2. The protocol approved by the IRB precluded such concomitant investigational agents or procedures. We reject your explanation for this item.

C. You did not obtain the ——— for later production of the investigational ——— according to the IRB-approved Protocol 2. The protocol required that ——— is collected by the use of a FDA-approved ——— You collected the ——— for subject — without using the specified device. The source of the blood for subject — is not documented.

Your response dated December 22, 1999, states that "initial drafts of Study #3 *[referenced as Protocol 2 in this letter]* allowed blood samples to be drawn by the Clinical Investigator." The protocol approved by the IRB does not permit the clinical investigator to obtain the blood sample in this manner.

D. Failure to perform follow-up visits at the required intervals. You did not examine the subjects at monthly intervals as required by Protocol 1.

Your response letter dated December 22, 1999, states that "treatment plans were constructed on an individual basis to balance patient needs with criteria of protocol procedure." FDA disagrees with your notion that clinical investigators may disregard the protocol requirements on a case-by-case basis.

4. Failure to maintain adequate and accurate case histories of individuals treated with the test drug. [21 CFR § 312.62(b)].

A. You did not maintain a roster identifying all subjects screened for possible participation in research with the investigational vaccine/serum, and did not maintain a list of all subjects who were subsequently enrolled. In your most recent periodic report to the IRB (IRB memo dated August 31, 1999), you stated that —subjects had been enrolled in Protocol 1.

Your response letter dated December 22, 1999, states that "study rosters are available for each clinical trial." However, you did not provide these to the FDA Investigator when asked to do so during the inspection. Please submit these rosters as part of your response to this letter.

B. You did not prepare or maintain a case report form for any subject. Subjects' medical charts did not specifically identify if a subject was participating in a study of an investigational product, or which protocol was applicable. Notations in the medical history do not constitute study data because the amount and type of clinical data are not sufficient to support analysis of safety and efficacy of investigational drugs. There is no documentation that study entry criteria are met, that protocol-required assessments are made, or whether adverse events occurred. The case report forms you were required to complete are included as attachments to Protocols 1 and 2.

Your response letter dated December 22, 1999, states that "Case Report Forms are available for all patients." However, you did not provide these to the FDA Investigator when asked to do so during the inspection.

Your response letter also states that you or a member of your office staff telephoned the subjects on two or three occasions during the first month to answer questions and to ensure that any adverse events would be documented and treated. You did not document that these calls were made, or whether adverse events occurred.

C. Records within subject files lack information regarding the usage of the test article. Subject records show that the test article was given to subjects, but there are no records indicating the amount and frequency of administration, the lot number of the product, and who administered the product to the subject. This is critical for Protocol 1 which permitted the subjects to self-administer the investigational vaccine/serum.

D. Protocols 1 and 2 specified that "all drugs administered or taken during the trial must be recorded on the case report form specifying the type of medication, dose, schedule, duration, and reason for use." This information was not recorded.

E. No objective measurements of efficacy were recorded for subjects in Protocols 1 and 2.

5. **Failure to retain records. [21 CFR § 312.62(c)].**

You did not retain the following records in your files:

A. Correspondence with the IRB. Missing IRB-related documents include consent forms, IRB approval letters, and progress reports.

Your response states that "complete IRB documentation for each study is available for FDA review." You failed to provide these documents when asked to do so during the FDA inspection.

B. A copy of the Protocol 1 titled ———————————————————

Although your response letter dated December 22, 1999, states that you have a copy of this protocol in your files, you failed to provide this protocol when asked to do so during the inspection.

C. Case histories. See item 4B, above.

D. Protocol 1 required that subjects complete a Quality of Life questionnaire on a monthly basis and for three months after the last treatment. Only one questionnaire was found in each of the files reviewed during the inspection.

E. Test article receipt and disposition records. See item 7, below.

Your response letter dated December 22, 1999, states that "all clinical Sponsor files for Study #1 and Study #2 *[referenced as Protocol 1 in this letter]* were removed when the studies were discontinued." You should have retained copies of the files that were removed by the sponsor.

6. **Failure to obtain Institutional Review Board review and approval of the protocol prior to treatment of human subjects and prior to implementing changes. [21 CFR §§ 312.66 and 56.103(a)].**

A. Protocol 2 was approved by the Great Lakes College of Clinical Medicine IRB on September 25, 1999. You administered the investigational ——— to at least one subject prior to IRB approval.

Your response letter dated December 22, 1999, states that the IRB approved this study "verbally on September 10, 1999." As documented in the letter from the IRB addressed to you, dated December 6, 1999, the IRB approved the study in the meeting held September 25, 1999. We reject your explanation for this violation.

B. You did not submit amended protocols to the IRB to permit you to administer concomitant investigational products to subjects. The IRB should have reviewed and approved an amended protocol before you administered concomitant investigational products to subjects. See item 3B, above.

7. **Failure to maintain adequate records of disposition of the investigational drugs. [21 CFR § 312.62(a)].**

You failed to maintain adequate records of distribution of investigational ——— used in Protocol 2, including the following:

A. An inventory of the amount, lot number and date of receipt from the manufacturer; and,

B. Dates and amounts of investigational ——— dispensed to each subject.

Your response letter dated December 22, 1999, explains that the manufacturer maintains these records, and that "the empty vials are returned per protocol directly to the manufacturing laboratory." According to Protocol 2, "the physician will receive a ninety-day supply of the investigational ——— clearly labeled, for each patient." The administration of the investigational product was to "occur under the physicians direct supervision." Since the product was to be administered in your office, the product would be in your possession, and, therefore, you are responsible for maintaining the records for receipt and dispensing of the investigational product.

8. **Failure to obtain informed consent in accordance with the provisions of 21 CFR Part 50. [21 CFR Part 50 and § 312.60].**

   A. The consent forms for Protocols 1 and 2 are deficient in the following areas:

      i. Use of the wording "You understand..." is inappropriate. The subjects may indicate that they understand particular general statements in the consent form and that answers have been provided by the consent process, but many will not comprehend the underlying scientific and medical significance of all the statements, nor are they in a position to judge whether the information provided is complete. Subjects should not be required to certify such understanding or completeness of disclosure.

      ii. The consent states "I understand ... that I may have a copy of this document." 21 CFR § 50.27(a) requires that a copy shall be given to the person signing the form.

      iii. The consent form does not contain the following required element: a description of any benefits to the subject or to others which may reasonably be expected from the research.

      iv. The consent form states, "Compensation for injuries as a result of participating in this study is not available except as may be required by law." It is not reasonable that prospective subjects would understand what is required by law. This phrase requires clarification.

   B. In addition to the deficiencies listed in item 8A, above, the consent form for Protocol 1 is deficient in the following areas:

      i. The consent form is written using technical language and medical jargon not readily understandable by a lay person, such as the terms ——— and "palliative."

ii. The consent form does not contain the following required elements:

a. An explanation of the procedures to be followed and the expected duration of the subject's participation. There is no explanation as to the role of x-rays in the study although radiation exposure is identified as a possible risk. There is no information as to the number of blood donations, the number, site, and timing of injections of the investigational product, who will perform the injections, the requirements of participants to travel, and any other procedures.

b. The identity of whom to contact in the event of research-related injury to the subject.

c. An explanation of whom to contact for answers to questions about research subjects' rights.

d. There is no description of the consequences of a subject's decision to withdraw from the study after it has begun.

iii. The consent form states that "information may be released to the Food and Drug Administration...." This statement is misleading since it implies that FDA has reviewed the research proposal, when, in fact, the study was not submitted to FDA in an IND at the time the subjects signed the consent forms.

C. In addition to the deficiencies listed in item 8A, above, the consent form for Protocol 2 is deficient in the following areas:

i. The consent form does not specifically identify the investigational product, and does not describe the procedures for obtaining the blood and tumor samples.

ii. The consent form states that "information may be released to the FDA." This statement is misleading since it implies that FDA has reviewed the research proposal when, in fact, this study has been conducted without an IND.

iii. The consent form is written using technical language and medical jargon not readily understandable by a lay person, such as the terms "anaphylaxis,' ——— ' and "autoimmunity."

iv. The consent form does not contain the following required element: an explanation of the procedures to be followed and the expected duration of the subject's participation. There is no information as to the number of blood donations, the number, site, and timing of serum injections, who will perform the injections, the requirements of participants to travel, and any other procedures.

vii. The informed consent form signed by Subjec[redacted] (Protocol 2) contained blanks on page 1 that were not completed.

This letter is not intended to be an all-inclusive list of deficiencies with your clinical studies of investigational adjuvant immune modulators. It is your responsibility to ensure adherence to each requirement of the law and relevant regulations.

On the basis of the above listed violations, FDA asserts that you have repeatedly or deliberately failed to comply with the cited regulations, and it proposes that you be disqualified as a clinical investigator. You may reply to the above stated issues, including an explanation of why you should remain eligible to receive investigational products and not be disqualified as a clinical investigator, in a written response or at an informal conference in my office. This procedure is provided for by regulation 21 CFR 312.70(a).

Within fifteen (15) days of receipt of this letter, write me to arrange a conference time or to indicate your intent to respond in writing. Your written response must be forwarded within thirty (30) days of receipt of this letter. Your reply should be sent to Mr. Steven A. Masiello, Office of Compliance and Biologics Quality HFM-600, Food and Drug Administration, 1401 Rockville Pike, Rockville, Maryland 20852-1448.

Should you request an informal conference, we ask that you provide us with a full and complete explanation of the above listed violations. You should bring with you all pertinent documents, and you may be accompanied by a representative. Although the conference is informal, a transcript of the conference will be prepared. If you choose to proceed in this manner, we plan to hold such a conference within 30 days of your request.

At any time during this administrative process, you may enter into a consent agreement with FDA regarding your future use of investigational products. Such an agreement would terminate this disqualification proceeding. Enclosed you will find a proposed agreement between you and FDA.

The Center will carefully consider any oral or written response. If your explanation is accepted by the Center, the disqualification process will be terminated. If your written or oral responses to our allegations are unsatisfactory, or we cannot come to terms on a consent agreement, or you do not respond to this notice, you will be offered the opportunity to request a regulatory hearing before FDA, pursuant to 21 CFR Part 16 (enclosed) and 21 CFR 312.70. Such a hearing will determine whether or not you will remain entitled to receive investigational products. You should be aware that neither entry into a consent agreement nor pursuit of a hearing precludes the possibility of a corollary judicial proceeding or administrative remedy concerning these violations.

Sincerely,

Steven A. Masiello
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation
and Research

Enclosures
21 CFR Part 16
21 CFR Part 312
21 CFR Part 50
Consent agreement